The Examiner has objected to the IDS filed on 8/02/01 a the IDS did not furnish titles of the cited reference C1-C65. Applicants have enclosed herewith a supplemental IDS (form 1449) including titles of the cited reference. Applicants request this objection be withdrawn.

2. Claim Rejections -- 35 U.S.C. § 112, second paragraph

Claim 1 has been rejected under 35 U.S.C. § 112, second paragraph for being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants have amended the claim to recite "atherosclerosis" rather than athersclerosis. Applicants request that this rejection be withdrawn.

3. Claim Rejections -- 35 U.S.C. § 102

A. Grubb et al

Claims 1 and 5-8 are rejected under 35 U.S.C. § 102(b) as being anticipated by Grubb et al (US Pat No. 5,037,957; "Grubb"). Applicants have canceled claim 5-8. Claim 1 has been amended and claims 15 and 16 are new. Applicants traverse this rejection to the extent it applies to the claims as amended.

The Examiner asserts that Grubb discloses a method of administering the cysteine protease inhibitor cystatin C to prophalatically treat ischemic injuries. Applicants disagree. Contrary to the Examiners assertion, Grubb does not disclose administering cystatin C to a subject. Rather, Grubb discloses administering a *10 amino acid peptide* based upon a segment of cystatin C.

The present invention discloses method of treating atherosclerosis by administering a cysteine protease inhibitor such as cystatin C. Applicants have amended claims 1 and added new claims 15 and 16 to clarify the patentable distinctions between the instant invention and the above-cited reference.

As amended, claim 1 recites a method of treating atherosclerosis comprising administering composition comprising *full length* cystatin C. Grubb does not teach nor suggest administering to a subject full length cystatin C as required by claim 1, thus Grubb does not anticipate claim 1 (or any of its dependent claims).

New claim 15 is directed to a method of treating or preventing atherosclerosis by administering to a subject a composition comprising SEQ ID NO: 3. Grubb does not teach or suggest the polypeptide of SEQ ID NO:3, thus Grubb does not anticipate claim 15.

New claim 16 is directed to a method treating or preventing atherosclerosis by identifying a subject suffering from or at risk of developing atherosclerosis and administering to the subject a composition comprising cystatin C. As discussed above, Grubb does not disclose administering full length cystatin C. Moreover, Grubb does not disclose administering cystatin C to a subject suffering from or at risk of developing atherosclerosis. In contrast Grubb discloses administering a 10 amino acid peptide to prevent ischemic injury. Ischemic injury causes irreversible cellular/tissue damage and cell death typically after an acute event. In contrast, the present invention is directed toward atherosclerosis-a chronic disorder characterized by the deposit of fatty material in the wall of the arteries. Thus, even if Grubb disclosed administering cystatin C to --which Applicants assert it does not for reasons discussed above--Grubb does not teach or suggest administering cystatin C to a subject suffering from or at risk of developing atherosclerosis. Thus, Grubb does not "read on" claim 16 and cannot anticipate that claim.

B. Iwata et al

Claims 13 and 14 are rejected under 35 U.S.C. § 102(b) as being anticipated by Iwata et al (US Pat No. 5,262,319; "Iwata"). Applicants amended claims 13 and 14. Applicants traverse this rejection to the extent it applies to the claims as amended.

According to the Examiner, Iwata discloses a method of treating a subject suffering from atherosclerosis by administering TGFβ. Applicants have amended claims 13 and 14 to recite TGFβ1. Iwata disclosure *specifically* recites administering TGFβ3 to treat atherosclerosis. (See Iwata column 8 line 21). Iwata *does not* teach or suggest administering to a subject TGFβ1 as required by amended claim 13 and 14. In fact, Iwata teaches away from using any other isoform of TGFβ besides TGFβ3. Iwata expressly states that the antibodies used specifically reacted with TGFβ3 and did not cross react with TGFβ1 or TGFβ2. (See, Iwata column 1, lines 57-58). Thus, Iwata does not anticipate claims 13 or 14 This rejection should be withdrawn.

4. Claim Rejections -- 35 U.S.C.§103(a)

A. Grubb/Emmanuel/Iwata

The Examiner has rejected claims 1, 5-14 over Grubb in view of Emmanuel et al.(US Pat No. 6,420,364; "Emmanuel") and Iwata. Applicants have cancelled claims 5-8 and, in view of the claim amendments, traverse the Examiner's rejection of claims 1, 9-14 and new claims 15 and 16.

Applicants have amended claims 1, 9-14 to clarify the patentable distinctions between the instant invention and the above-cited references.

As a preliminary matter, there is no suggestion to combine Grubb, Emmanuel and Iwata to produce the claimed invention. Grubb merely refers a 10 amino acid peptide based on cystatin C to prevent ischemic related tissue damage, Emmanuel refers cysteine protease inhibitors, and Iwata refers treating atherosclerosis by administering TGFβ3 . Furthermore, even if combined (which applicants do not believe is proper) that combination does not teach or suggest the claimed methods of treating or preventing atherosclerosis by administering cystatin, SEQ ID NO:3 or TGFβ1—as the claims as amend require.

Grubb is critically deficient. Grubb describes a 10 amino acid peptide that was based on cystatin C The identified peptide was capable of inhibiting protease enzyme activity. Grubb does not teach or suggest using full length cystatin C, the polypeptide of SEQ ID NO:3, or TGFβ1 to treat or prevent a chronic coronary disorder- atherosclerosis, as required by the amended claims.

Emmanuel does not cure these deficiencies. Emmanuel describes novel cathepsin S, K< L and B inhibitors and there use for treating atherosclerosis. Emmanuel does not suggest that cystatin C the polypeptide of SEQ ID NO:3, or TGFβ1 should be administered to a subject to treat atherosclerosis. Therefore, the combination of Grubb and Emmanuel cannot lead the ordinarily skilled artisan to the claimed methods.

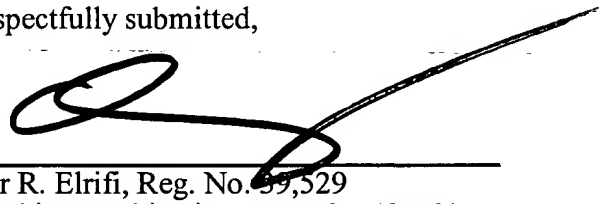
Further, the combination of Grubb and Emmanuel with the Iwata does not render obvious the claimed invention. Iwata teaches the use of TGFβ3 to treat atherosclerosis. Iwata does not teach the use of cystatin C, the polypeptide of SEQ ID NO:3, or TGFβ1 to treat atherosclerosis as is required in the amended claims.

Even assuming that the combination of Grubb, Emmanuel and Iwata could be made, that combination would not lead the ordinarily skilled artisan to the claimed methods of treating or preventing atherosclerosis by administering cystatin C, the polypeptide of SEQ ID NO:3, or TGFβ1. Therefore, Applicants assert that the rejection should be withdrawn.

CONCLUSION

Applicants believe that the claims, as amended, are in condition for allowance. If the Examiner has any questions, the Examiner is invited to contact the undersigned by telephone.

Respectfully submitted,



Ivor R. Elrifi, Reg. No. 39,529
Cynthia Kozakiewicz, Reg. No. 42,764
Attorneys for Applicants
c/o MINTZ, LEVIN
One Financial Center
Boston, Massachusetts 02111
Tel: (617) 542-6000
Fax: (617) 542-2241

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Version with Markings to Show Changes

1. A method of treating [atherosclerosis] atherosclerosis in a subject, comprising administering to said subject [an inhibitor of a cysteine protease] a composition comprising cystatin C.

9. The method of claim 1, wherein said inhibitor is administered [locally to a site of vascular injury] directly to an atherosclerotic plaque.

10. The method of claim 1, wherein said [inhibitor] composition is administered systemically.

11. A method of preventing development of [atherosclerosis] atherosclerosis in a subject, comprising administering to said subject [an inhibitor of a cysteine protease] a composition comprising cystatin C.

12. The method of claim 11, wherein said subject is at risk of developing [atherosclerosis] atherosclerosis.

13. A method of treating [atherosclerosis] atherosclerosis. in a subject, comprising administering to said subject transforming growth factor beta 1.

14 A method of preventing development of a [atherosclerosis] atherosclerosis. in a subject, comprising administering to said subject transforming growth factor beta 1.